A Proposal for a New Direction to Treat Cancer

Sam Rose
Oncologic Inc

A new approach is proposed that has the potential to be a successful therapy for most disseminated cancers because it can circumvent the problems posed by three characteristics which are universally expressed by cancer cells: heterogeneity, plasticity, and the lack of a cancer specific or cancer associated characteristic which is not also shared by some normal cells.

Analysis shows that almost all current and research approaches for treating disseminated cancers have the same fundamental strategy: they rely on an agent interacting individually and effectively with each cancer cell. We call all these approaches "lock and key" strategies to emphasize the need for this individual agent to cell interaction. The three characteristics preclude current approaches from successfully treating most disseminated cancers because they operate by a "lock and key" strategy which (a) only kills cancer cells expressing a single particular trait, (b) allows other cancer cells to adapt and survive the treatment, and (c) also kills the normal cells which express the same particular trait.

The heterogeneity and plasticity of cancer cells can only be circumvented by an attack which is microregional (not cell by cell) and destructive (not killed by conventional endogenous or exogenous cytotoxic agents). All cells in each microregion must be destroyed, including those which do not express an exploitable trait. The proposed approach can achieve such microregional destruction (a trait independent form of killing) by the delivery to, and long term immobilization of a large number of radio-isotopes. This is achieved by an immuno-enzymatic amplification system which uses a low number of labile natural receptors to construct a large number of stable, foreign, uniquely targetable, surrogate receptors on an insoluble platform. It is from these surrogate receptors that the attack against the cancer is launched.

The proposed approach exploits the additive contribution of multiple mechanisms to enhance tumor specificity of the microregions. Given that all targeting and killing agents are "imperfect" this is the only way specificity can be enhanced. The biological basis of these specificity enhancing mechanisms are well-known. However, they are ignored by current therapies because most of them can only be exploited in the context of the proposed approach. Some of the mechanisms reflect characteristics, such as heterogeneity, genetic instability, and tumor progression which are the result of the micro-evolutionary process of tumor development. These are virtually always present in, and virtually specific to cancer. Others reflect the somewhat "imperfect" cancer associated characteristics of structures, including cancer cells, extracellular structures, and non-malignant cells, within the tumor mass. The additive contribution of the multiple mechanisms gives the process the potential to destroy all the cancer cells with minimal non-tumor toxicity.

The cornerstone of the proposed approach is a novel class of soluble chemicals. They can be administered intravenously to subjects, circulate throughout body fluids and are enzymatically converted into an insoluble material when the chemicals reach targeted sites. In this paper, these chemicals are called "soluble precipitable reagents"(SPR) to

describe their ability to be converted from a soluble to an insoluble material. The insoluble material is called platform and has surrogate receptors which have the ability to bind various agents (non-covalently or covalently) with high affinity, high specificity, and long term retention. The SPR chemicals enable a 3-step process to be constructed which can deliver and retain a large number of radio-isotope atoms in tumor tissue (fig 1).

In step 1, a binary reagent comprised of an SPR attached to an imperfect cancer targeting agent is administered. The binary reagent is endocytosed and transported into lysosomes where the targeting agent moiety is digested and the detached SPR is converted by natural intracellular lysosomal enzymes into an insoluble platform having surrogate receptors. As will be discussed, a very large number of platform molecules, and hence a large number of surrogate receptors, can be made to accumulate inside targeted cells.

In step 2, a supersensitive fraction of the cancer cells, including some which had accumulated platform in step 1, are killed by the administration of a very low dose of an anti-cancer agent. Very few, if any, normal cells will be killed by the very low dose. The death of the cells relocates the accumulated platform into the extracellular tissue fluid. After a lapse of time, any platform which is still retained in the extracellular tissue fluid can proceed to step 3.

In step 3, the surrogate receptors on the platform are used by one of two different methods to generate supra-lethal radiation fields. This is achieved in the first method by the binding and long term retention of a large number of isotope-carrying molecules to the surrogate receptors on the extracellular platform. In the second method, a bispecific reagent, having a non-mammalian enzyme moiety is bound to the platform. The bound enzyme converts a subsequently administered free (non-targeted) radioactive SPR into an insoluble radioactive second precipitate which remains adjacent to the bound enzyme for a long time. Both methods, thus, result in the immobilization and long term retention of a large number of isotope atoms in the tumor tissue, thereby generating intense radiation fields which cause microregional destruction of thousands of neighboring cells.